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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/071,962	02/08/2002	Baofu Ni	TNX 98-03-01	2802

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EXAMINER	
SPECTOR, LORRAINE	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 01/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/071,962	NI ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2005 and 20 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-33,36-41 and 44-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-33,36-41,45 and 48-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *31-33,36-41 and 44-50* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the arguments filed 6/30/2005, and the claims filed 10/20/2005. Claims 31-33, 36-41 and 44-50 are pending. Claims 31-33, 36-41, 45 and 48-50 are under consideration.

Claim Interpretation

Newly submitted claim 48 contains a product-by-process limitation regarding how the antibody was made. While not *per se* indefinite, it is noted that product-by-process limitations are given weight only to the extent that the affect the product being claimed. Antibodies are generally considered to be fully defined by their binding properties, in this case to "specifically bind(s) or interact with human G-CSF receptor" (although the latter limitation is itself indefinite, see below), thus making the product-by-process limitation irrelevant.

The language of claim 49 states in part "The agonist antibody of claim 31 wherein the antibody comprises..." "a functional variant of any one of SEQ ID NOs 15 to 20. This allows variation in all six CDRs, and thus reads on any agonist antibody that binds human G-CSF.

With regard to claim 50, "framework" is an inherent part of the structure of an antibody, and accordingly requires no antecedent basis in the independent claim.

Claim Objections

Claims 39 and 41 are objected to for reciting a non-elected species. Correction is required. Applicants have requested that this requirement be held in abeyance. Applicants are reminded that they are only entitled to rejoinder of non-elected species in the event that a generic claim is found allowable. There are no allowable generic claims at this time.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39 and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The enablement of claim(s) 39 and 41 requires availability of the specific hybridomas or antibodies claimed therein. This determination has been made because said hybridomas and antibodies are not fully disclosed nor have they been shown to be publicly known and freely available. Accordingly, it is deemed that a deposit these hybridomas should have been made in accordance with MPEP Chapter 2400 and 37 C.F.R.§§1.801-1.809. Applicant is advised that the Patent Office accepts Budapest approved deposits, as long as assurance is provided that the deposited material will be made irrevocably available with no restrictions upon issuance of a patent. See MPEP Chapter 2400 at 2414.01.

The amendment to the specification dated 6/30/2005 is noted, as is applicants argument that a copy of the ATCC deposit receipt was to be enclosed with that response. This argument has been fully considered but is not deemed persuasive because it remains that the terms of deposit have not been disclosed, and the ATCC receipt did not accompany the response.

Claims 48 and 50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for G-CSF agonist antibodies that bind to the extracellular portion of G-CSF receptor, provides *neither* adequate written description nor enablement of G-CSF agonist antibodies that bind to the *intra*cellular portion of G-CSF receptor. The specification does not provide an adequate written description of such antibodies, nor does it enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. This rejection is maintained for reasons of record regarding Claims 31-33, 37, 38, 40 and 45 in the previous Office Action.

The art appreciates that it does not require undue experimentation to make agonist antibodies to a given receptor, including to the G-CSF receptor (see art rejections, below). However, as evidenced by that patents cited below, the art teaches that such antibodies bind to

the *extracellular* domain of the receptor, which is that portion of the receptor to which G-CSF, the 'natural' agonist binds. The Examiner is unable to find any reports in the art of antibodies that act as receptor agonists, which bind to the *transmembrane or intracellular* portion of the receptor. As claim 34 specifically recites that the claimed antibodies bind to the extracellular portion, the Examiner concludes that applicants intend claims 31-33, 37, 38, 40 and 45 to specifically encompass antibodies that do *not* bind to the extracellular domain, i.e. bind to the transmembrane or intracellular domains of the receptor. As the art does not recognize that such antibodies would have the required function, and as the specification provides neither any written description of such antibodies, nor any guidance or working examples of such, the Examiner concludes that the written description in the specification is not adequate to support such claims, and further, that undue experimentation would be required to practice such an invention in a manner commensurate in scope with the claims.

Claim 38 remains rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for fragments of antibodies that bind bivalently, does not reasonably provide enablement for monovalent fragments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Dimerization of G-CSF receptor is required for activation and signaling to occur. In fact, the specification as filed teaches at page 3, that "Homodimerization of the G-CSF receptor has been shown to be essential for signal transduction (Wells, J. A., and Vos, A. M., Annu. Rev. Biochem.,1996,65: 609)." U.S. Patent Number 5,506,107 (Cunningham et al.) teaches at column 24 that "monovalent antibodies, which only bind to one receptor molecule, are useful as antagonists." Accordingly, those species recited in claim 38 that are monovalent would be expected, in view of the specification and the art, not to be agonist antibodies. The specification provides no guidance or working examples, of how to make monovalent agonist antibodies, nor how to use monovalent antagonist antibodies in a fashion that would result in agonist activity. Accordingly, in view of the specification and the art, the Examiner concludes that it would

require undue experimentation to practice the invention in a manner commensurate in scope with claim 38.

Applicants argue that the fragments of claim 38 are useful because after administration, more than one fragment may bind to the receptor resulting in dimerization. This argument has been fully considered but is not deemed persuasive because binding of more than one fragment would *not* result in dimerization of the receptor. In fact, it would be likely to *inhibit* such (were it otherwise be inclined to occur), by preventing two receptors from being able to achieve sufficient proximity in the cell membrane. Binding of two fragments to a single receptor is not the same thing as receptor dimerization. Further, even *if* applicants argument were factually correct, the individual fragments themselves would not meet the limitations of claims 31 or 32.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 31-33, 36-38, 40, 45 and 48-50 are rejected under 35 U.S.C. 102(b) as being anticipated by Cunningham et al., US Patent No. 5,506,107.

Cunningham et al. disclose the production of agonist antibodies which are capable of stimulating receptors for various ligands. Production of agonists which stimulate the G-CSF receptor is specifically mentioned at column 12 line 56. At columns 23-24, Cunningham et al. discuss agonist antibodies to the growth hormone receptor, and state that such antibodies may be raised by immunizing animals against growth hormone (and presumably screening the resultant antibodies for agonist properties). Also at columns 23-24, Cunningham et al. disclose such antibodies to be monoclonal, chimeric, or CDR grafted, and compositions comprising such

antibodies. The person of ordinary skill in the art would immediately grasp CDR grafted antibodies as disclosed by Cunningham et al. as meaning humanized, as in newly submitted claim 50. The screening methods for identification of agonist antibodies are disclosed at columns 36-39. Thus, Cunningham discloses the desirability of obtaining agonists of the G-CSF receptor, and further discloses methods of obtaining agonist antibodies consistent with the claims. Accordingly, Cunningham et al. fairly place the claimed invention in the hands of the public.

Applicants argue that Cunnningham does not anticipate the claims because they did not actually make antibodies, and because one would have to screen several antibodies to find an agonist. This argument has been fully considered but is not deemed persuasive because at column 23, Cunningham clearly states:

> We have determined that certain antibodies are capable of stimulating the hGH receptor, i.e., they are capable of crosslinking the receptors in a fashion that mimics the ability of hGH to form a ternary complex and activate the receptor. Examples of such agonist antibodies were already known at the time of this invention, but their ability to act as agonists of hGH was unappreciated. Suitable antibodies are MAb 263 (Barnard, et al., Endocrinology, 115:1805-1813 [1984] or Barnard, et al., Biochem. J., 231:459-468 [1985]). Others are MAbs 13E1 and 3D9, produced by methods described below.

Further, Cunningham confirmed the agonist antibody activity *in vivo*, see column 36.

Thus, Cunningham clearly not only discloses having such antibodies, but that they were already available in the prior art. The Examiner notes that determination of a property of a compound that was already known does not make the compound newly patentable, as a compound and its properties are inseparable.

With further respect to applicants arguments regarding how to screen for antibodies within the scope of the claims, the Examiner notes that such is routine experimentation in the art. This position is supported by the finding in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), in which the court reversed the rejection for lack of enablement under 35 U.S.C. 112, first paragraph, concluding that undue experimentation would not be required to practice the

invention, and by *In re Graves*, 36 USPQ 2d1697 at 1701 which held that a reference. anticipates a claim if it discloses the claimed invention "such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention."

Claims 31-33, 36-38, 40, 45 and 48-50 are rejected under 35 U.S.C. 102(b) as being anticipated by Adams et al., US Patent No. 6,342,220.

Adams et al. disclose the production of agonist antibodies which are capable of stimulating receptors for various ligands. Production of agonists which stimulate the G-CSF receptor is specifically mentioned at column 12 line 56. Fragment and single chain antibodies are discussed at column 18. Methods of making the antibodies are disclosed at column 25. Thus, Adams discloses the desirability of obtaining agonists of the G-CSF receptor, and further discloses methods of obtaining agonist antibodies consistent with the claims. Accordingly, Adams et al. fairly place the claimed invention in the hands of the public.

Applicants traversal of this rejection has been fully considered but is not deemed persuasive for reasons cited above.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

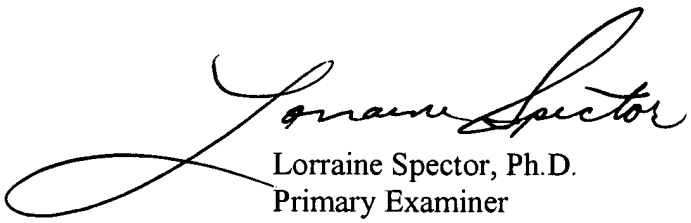
Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to 571-273-8300. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Lorraine Spector, Ph.D.
Primary Examiner